STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 107731

TO:	From:
Michael Meller **Location: cm1/10A03** **Art Unit: 1654** **Wednesday, November 05, 2003** **Case Serial Number: 10/026408**	**Mary Hale** **Location: Biotech/Chem Library** **CM1-1E01** **Phone: 308-4258** **Mary.Hale@uspto.gov**

Search Notes

Exmr. Meller-

Example 1 was searched. Refer to structure drawing, you'll see what components were drawn.

25 structures were retrieved all having one EP patent reference.

Displayed all structures.

Hope this works for you.

Mary

Mary Hale – Supervisor, Info. Branch
STIC – Biotech/Chem. Library
CM-1 Room E01
703-308-4258

* Rush Request - Amanda (ASC) Access DB# 107731

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Michael Miller Examiner #: 69404 Date: 11/5/03
Art Unit: 1654 Phone Number 308-4230 Serial Number: 10/026,408
Mail Box and Bldg/Room Location: CM1 10A03 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): Lerchen, Hans-Georg; Baumgarten, Jörg; Lockhoff, Oswald; Albers, Markus; Schoop, Andreas.

Earliest Priority Filing Date: 12/27/2006

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please Search this Specific Compound.

Do not expand its structure.

Only this compound highlighted.

Example 2: -7500 Attached sheet.

1429
14:19

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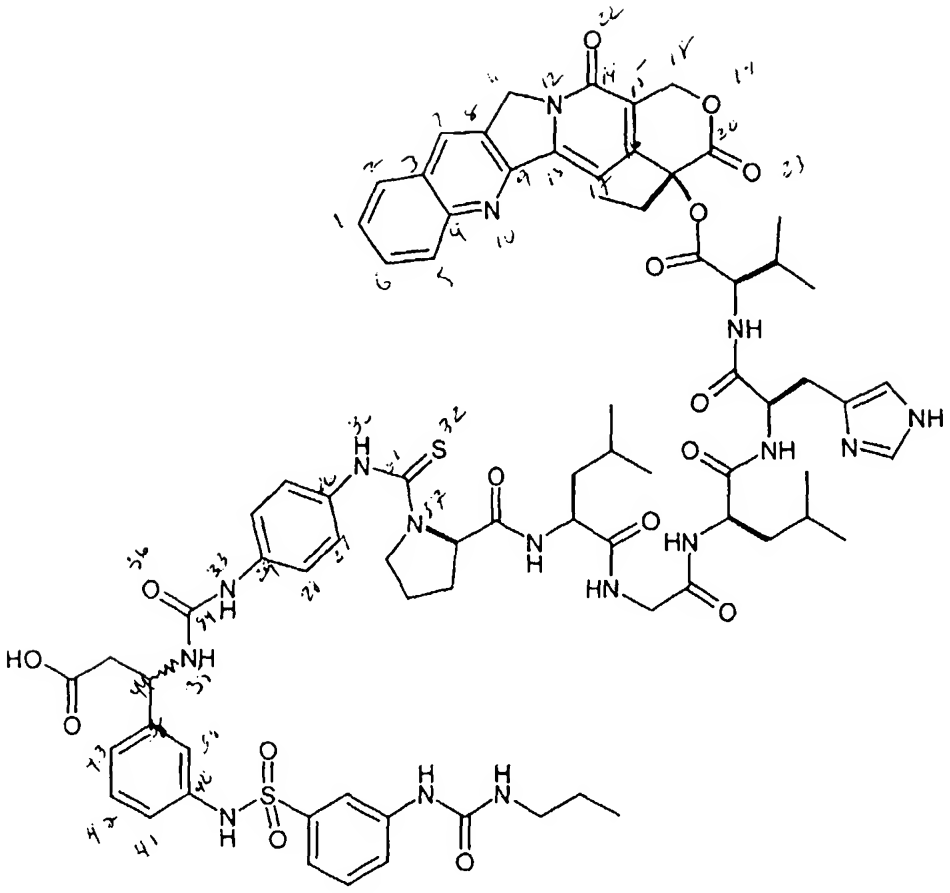
STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: Mary	NA Sequence (#)	STN 256.11
Searcher Phone #: 8-4258	AA Sequence (#)	Dialog
Searcher Location: 1E71	Structure (#) 1	Questel/Orbit
Date Searcher Picked Up:	Bibliographic	Dr Link
Date Completed: 11/5	Litigation	Lexis/Nexis
Searcher Prep & Review Time: 7	Fulltext	Sequence Systems
Clerical Prep Time: 4	Patent Family	WWW/Internet
Online Time: 10	Other	Other (specify)

PTO-1590 (8-01)

Example 1:



Educts: II.1, III.1 Procedure: A

Yield: 71% $R_f = 0.28$ [6] [ESI-MS: m/e = 1561 = $(M+H)^+$]

Example 2: Diastereoisomer A of compound from Example 1

Educts: II.1, III.2 Procedure: A

Yield: 32% $R_f = 0.28$ [6] [ESI-MS: m/e = 1561 = $(M+H)^+$]

Miller
10/026408

=> dis his

(FILE 'HOME' ENTERED AT 14:19:44 ON 05 NOV 2003)

FILE 'REGISTRY' ENTERED AT 14:19:50 ON 05 NOV 2003
L1 STR
L2 0 S L1
L3 25 S L1 FUL

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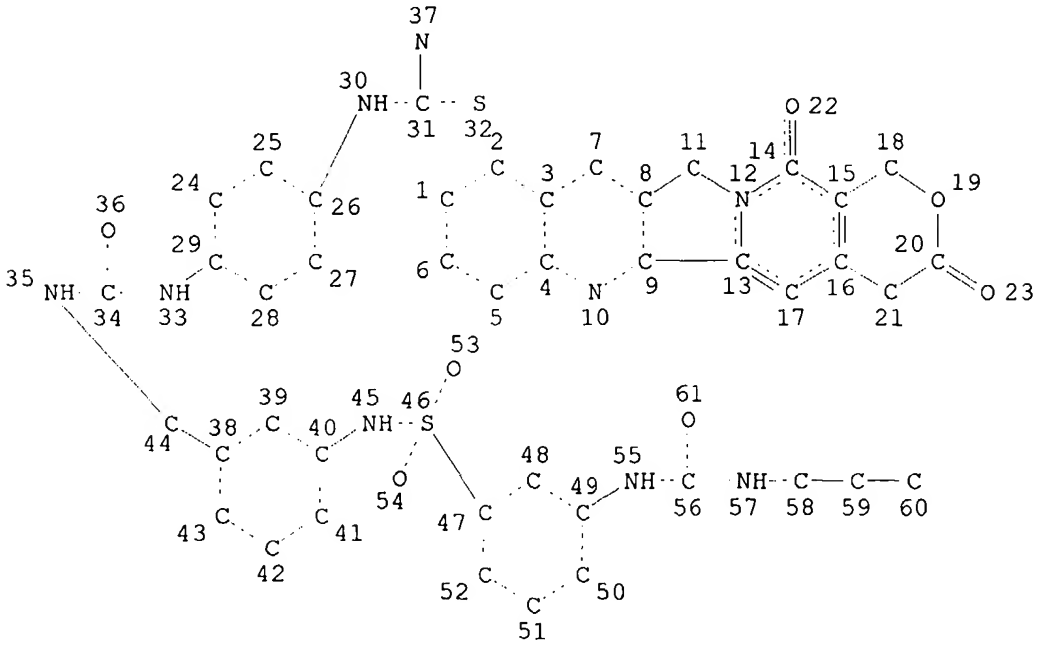
L1 STR



NODE ATTRIBUTES:
NSPEC IS R AT 37
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 61

STEREO ATTRIBUTES: NONE
L3 25 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 46 ITERATIONS 25 ANSWERS
SEARCH TIME: 00.00.01

L3 ANSWER 1 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439865-01-7 REGISTRY
CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-L-prolyl-, 6-[(4S)-4-ethyl-

Searched by: Mary Hale 308-4258 CM-1 1E01

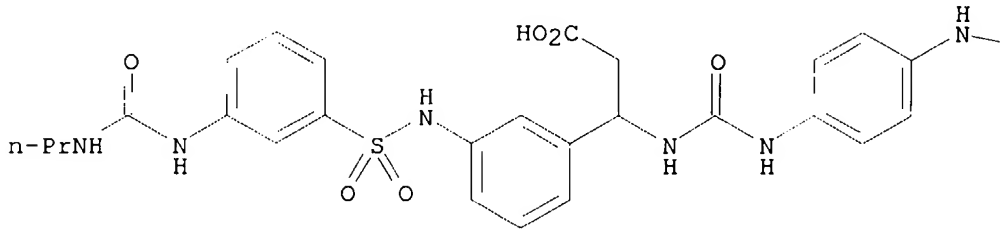
3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)

FS PROTEIN SEQUENCE; STEREOSEARCH
MF C76 H92 N14 O16 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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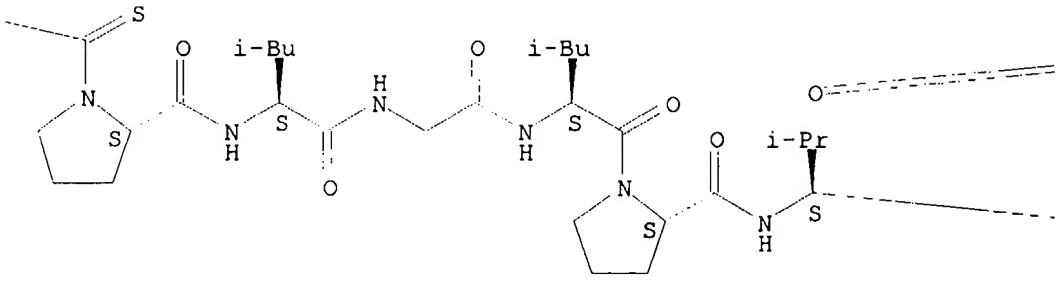
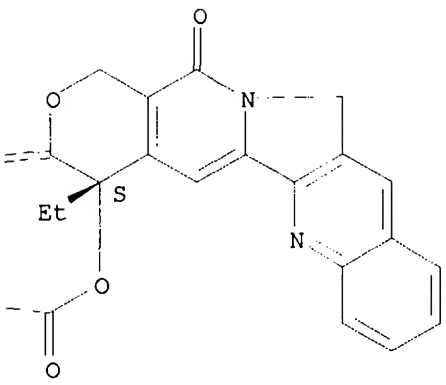


Searched by: Mary Hale 308-4258 CM-1 1E01



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:63479 Preparation of conjugates of integrin receptor antagonists and a cytostatic agent having specifically cleavable linking units. Lerchen, Hans-Georg; Baumgarten, Joerg; Lockhoff, Oswald; Albers, Markus; Schoop, Andreas (Bayer Aktiengesellschaft, Germany). Eur. Pat. Appl. EP 1219305 A1 20020703, 127 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2000-128401 20001227.

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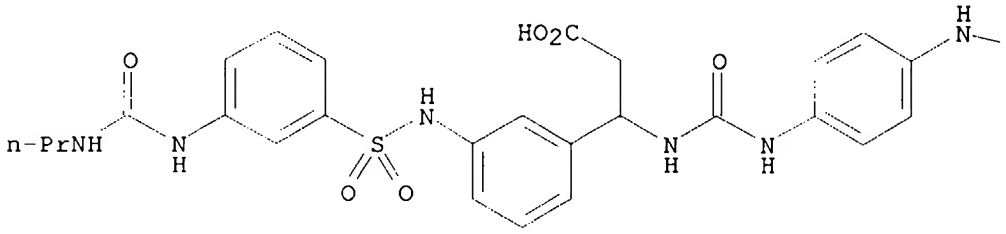
Searched by: Mary Hale 308-4258 CM-1 1E01

L3 ANSWER 2 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439865-00-6 REGISTRY
CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucylglycyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C73 H88 N14 O16 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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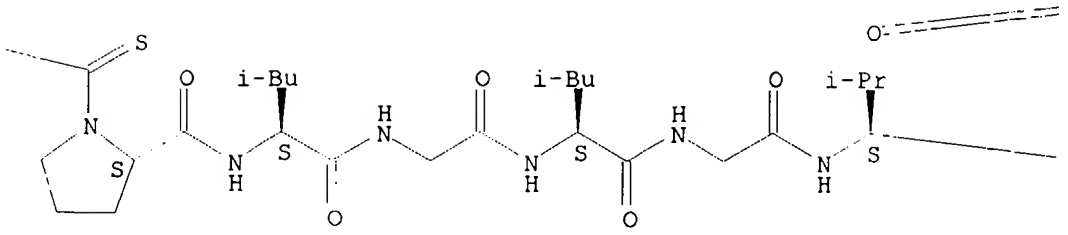
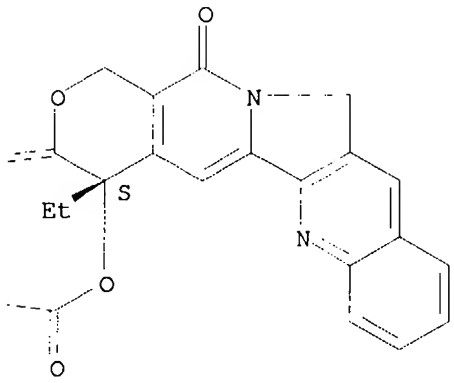


Searched by: Mary Hale 308-4258 CM-1 1E01



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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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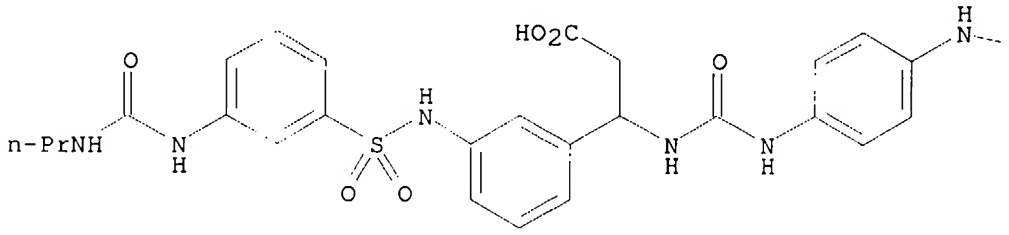
AB The invention relates to cytostatics CT-LI-Sp-IA [CT denotes a cytotoxic radical or a radical of a cytostatic or a cytostatic derivative which can addnl. carry a hydroxy, carboxy or amino group; LI is a linker group comprising 5- to 8-amino acid residues in the D- or L-configuration, which can each optionally carry protective groups; Sp is absent or a carbonyl or thiocarbonyl radical; IA is a non-peptide radical addressing an αvβ3 integrin receptor, e.g., a radical of formula R18COCH2CHPhNHCOCH2NHCO-m-C6H4NH[C(:NH)NHR19]q, where R18 is OH, (un)substituted (cyclo)alkoxy, aryloxy, heterocyclyloxy, a direct bond, or an atom from the group N, O and S, via which the radical is bonded to the rest of the conjugate; q is 0 or 1; R19 is H, (un)substituted (cyclo)alkyl, aryl, heterocyclyl, an alkylamine or alkylamide radical, or a direct bond, via which the radical is bonded to the rest of the conjugate] and their physiol. acceptable salts and stereoisomers. The cytostatics have a tumor-specific action as a result of linkage to αvβ3integrin antagonists via preferred linking units which can be selectively cleaved by enzymes such as metallo matrix proteases (MMPs5), i.e., by enzymes which can especially be found in tumor tissue. The preferred linking units guarantee the serum stability of the conjugate of cytostatic and αvβ3 integrin antagonist and, at the same time, the desired intracellular action within tumor cells as a result of its specific enzymic or hydrolytic cleavability with release of the cytostatic. Thus, 20-O-[PrNHCONH-m-C6H4SO2NH-m-C6H4CH(CH2CO2H)NHCONH-p-C6H4NHC(S)-Pro-Leu-Gly-Leu-His-Val]camptothecin (1) was prepared by reaction of 20(S)-camptothecin with N-(tert-butoxycarbonyl)-L-valine-N-carboxyanhydride, deprotection, peptide coupling reactions, and formation of the thiourea linkage. Compound 1 was assayed for cytostatic action on human large intestine cell line HT29 (IC50 = 40 nM).

L3 ANSWER 3 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-99-0 REGISTRY
CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-L-α-glutamyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C76 H92 N14 O18 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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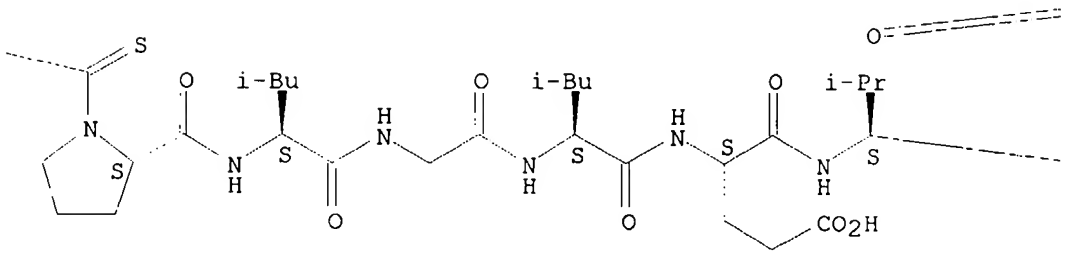
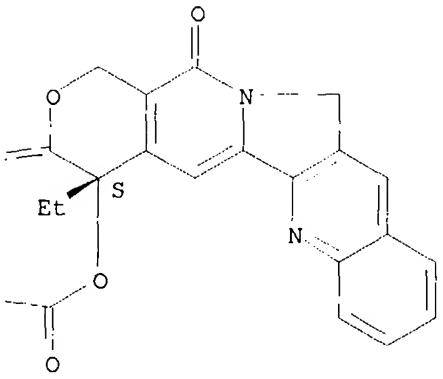


Searched by: Mary Hale 308-4258 CM-1 1E01



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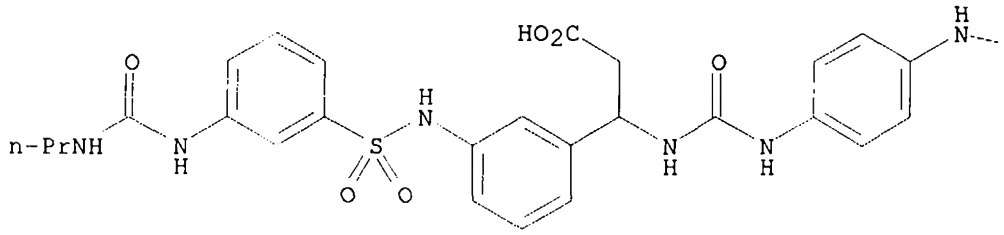
L3 ANSWER 4 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-98-9 REGISTRY
CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-L-isoleucyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C77 H96 N14 O16 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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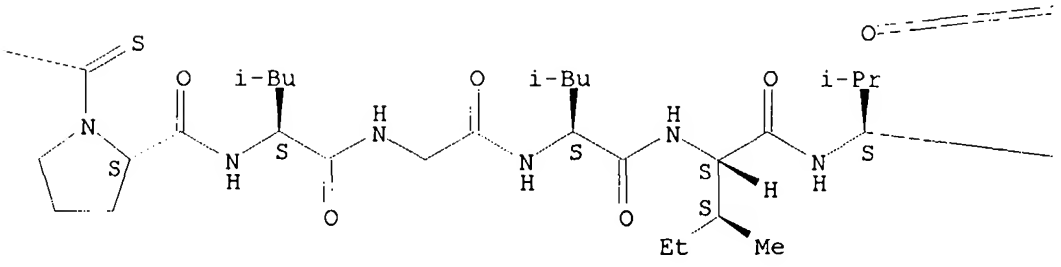
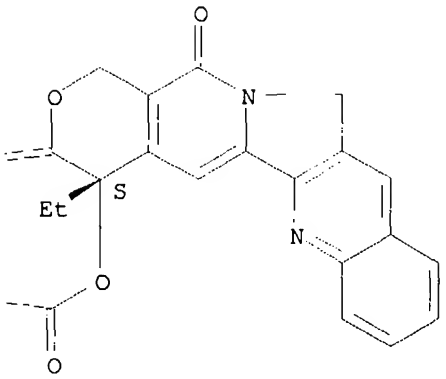


Searched by: Mary Hale 308-4258 CM-1 1E01



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L3 ANSWER 5 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-97-8 REGISTRY

Searched by: Mary Hale 308-4258 CM-1 1E01

CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-L-seryl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)

FS PROTEIN SEQUENCE; STEREOSEARCH

MF C74 H90 N14 O17 S2

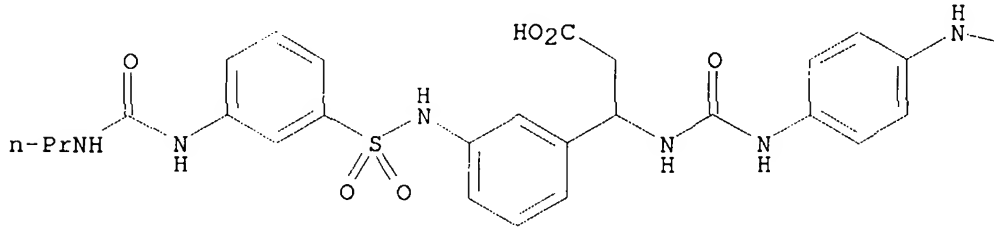
SR CA

LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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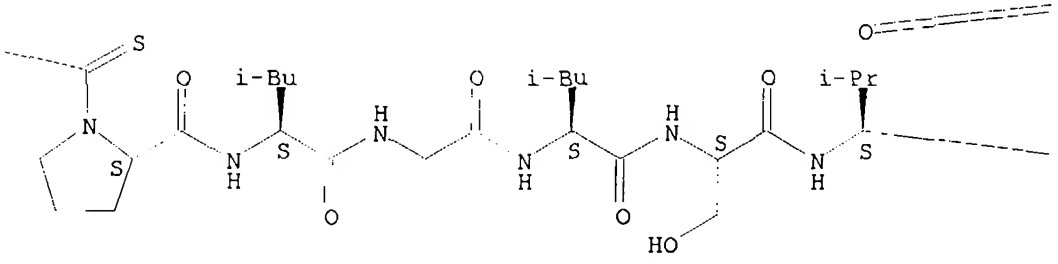
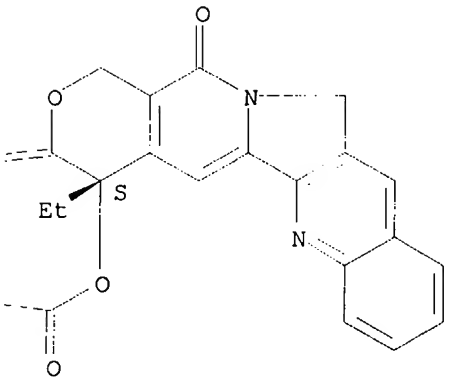


Searched by: Mary Hale 308-4258 CM-1 1E01



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:63479 Preparation of conjugates of integrin receptor antagonists and a cytostatic agent having specifically cleavable linking units. Lerchen, Hans-Georg; Baumgarten, Joerg; Lockhoff, Oswald; Albers, Markus; Schoop, Andreas (Bayer Aktiengesellschaft, Germany). Eur. Pat. Appl. EP 1219305 A1 20020703, 127 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2000-128401 20001227.

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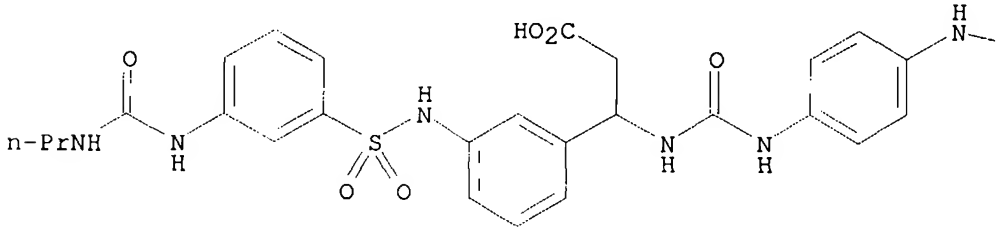
L3 ANSWER 6 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-96-7 REGISTRY
CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-L-phenylalanyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C80 H94 N14 O16 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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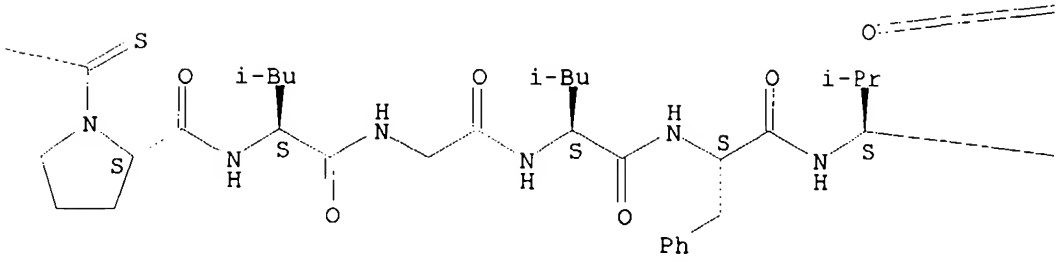
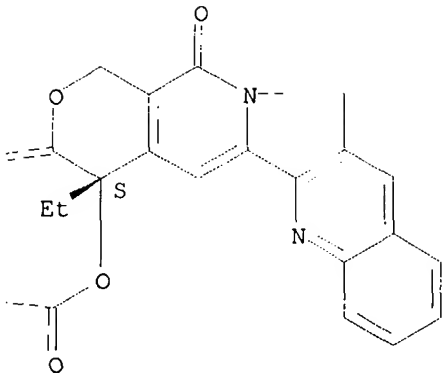


Searched by: Mary Hale 308-4258 CM-1 1E01



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:63479 Preparation of conjugates of integrin receptor antagonists and a cytostatic agent having specifically cleavable linking units. Lerchen, Hans-Georg; Baumgarten, Joerg; Lockhoff, Oswald; Albers, Markus; Schoop, Andreas (Bayer Aktiengesellschaft, Germany). Eur. Pat. Appl. EP 1219305 A1 20020703, 127 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2000-128401 20001227.

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L3 ANSWER 7 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-95-6 REGISTRY

Searched by: Mary Hale 308-4258 CM-1 1E01

CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-L-valyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)

FS PROTEIN SEQUENCE; STEREOSEARCH

MF C76 H94 N14 O16 S2

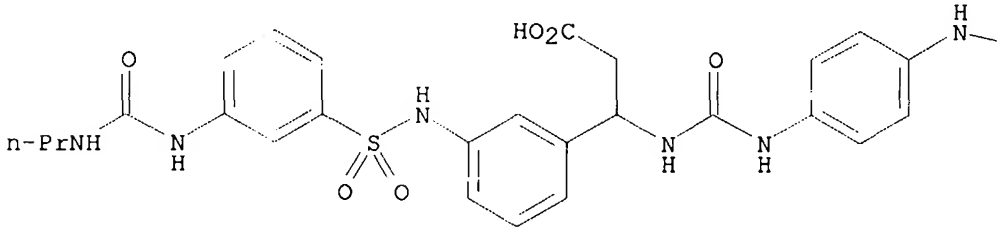
SR CA

LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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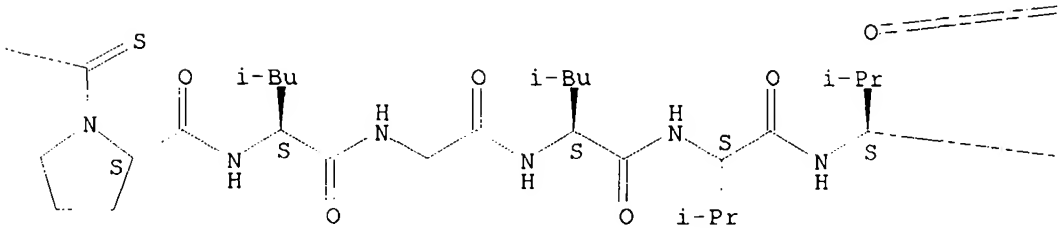
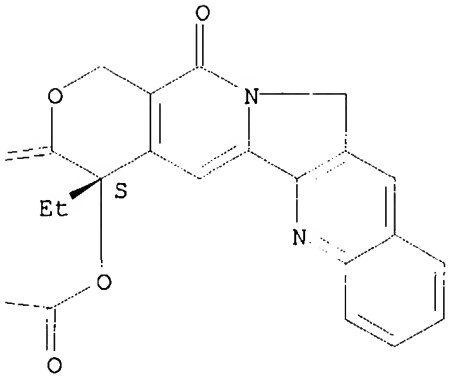


Searched by: Mary Hale 308-4258 CM-1 1E01



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L3 ANSWER 8 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-94-5 REGISTRY

Searched by: Mary Hale 308-4258 CM-1 1E01

CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-D-alanyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)

FS PROTEIN SEQUENCE; STEREOSEARCH

MF C74 H90 N14 O16 S2

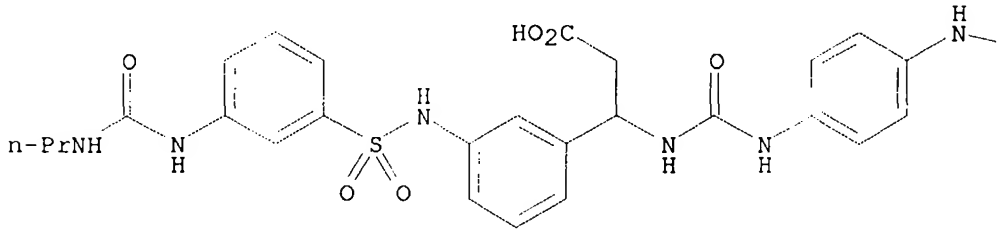
SR CA

LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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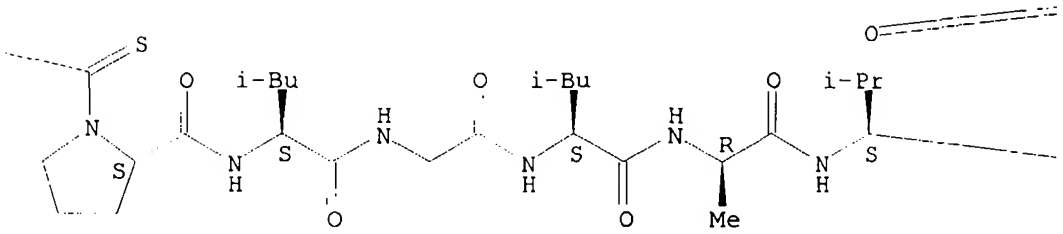

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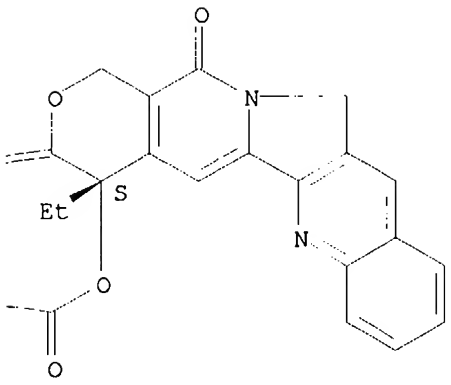

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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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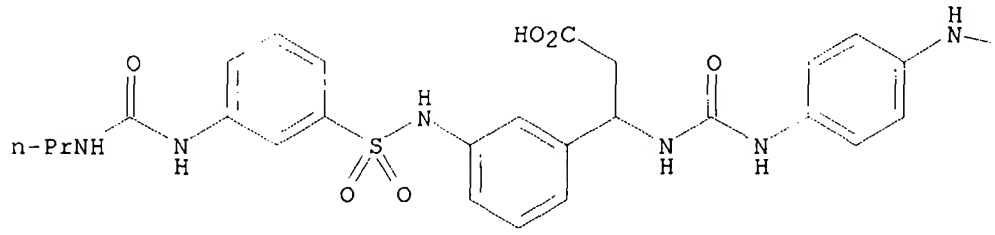
L3 ANSWER 9 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-93-4 REGISTRY
CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-L-alanyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C74 H90 N14 O16 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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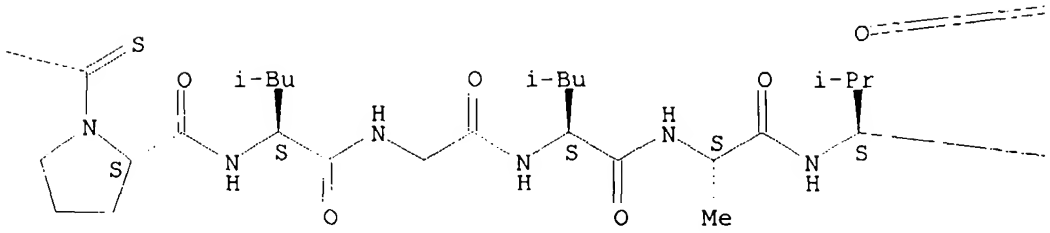
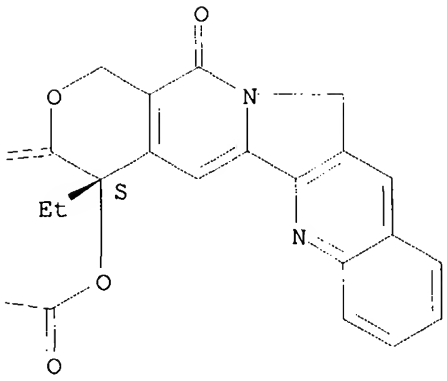


Searched by: Mary Hale 308-4258 CM-1 1E01



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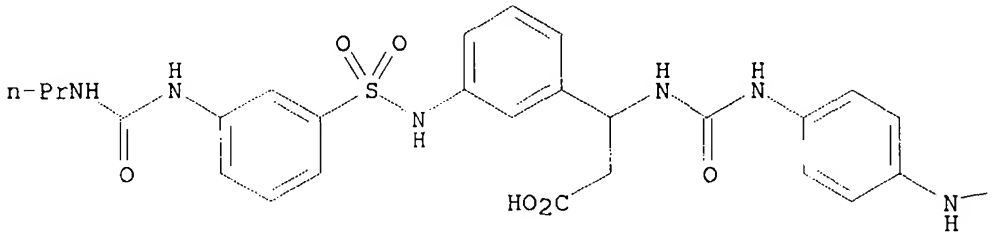
Searched by: Mary Hale 308-4258 CM-1 1E01

L3 ANSWER 10 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-91-2 REGISTRY
CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-prolyl-L-leucylglycyl-L-leucyl-L-asparaginyl-, 7-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C80 H98 N16 O18 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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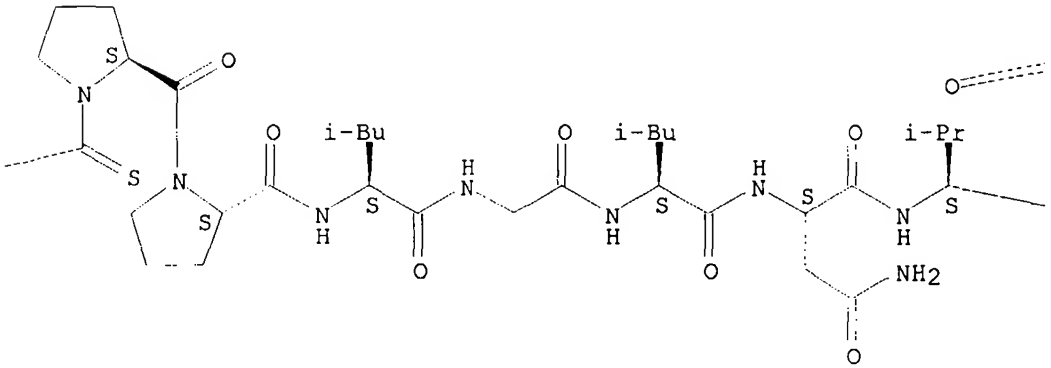

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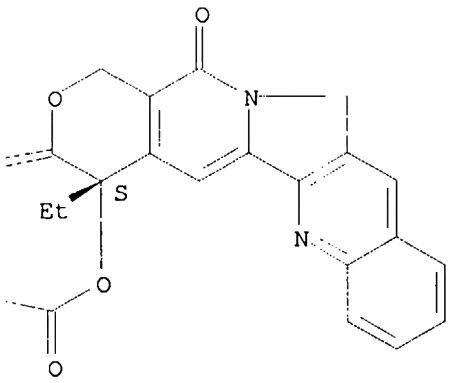

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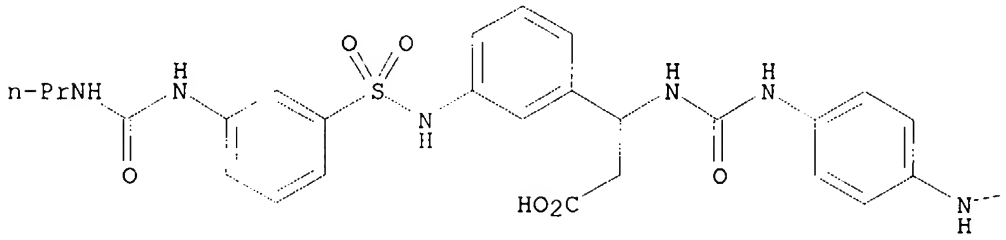
AB The invention relates to cytostatics CT-LI-Sp-IA [CT denotes a cytotoxic radical or a radical of a cytostatic or a cytostatic derivative which can addnl. carry a hydroxy, carboxy or amino group; LI is a linker group comprising 5- to 8-amino acid residues in the D- or L-configuration, which can each optionally carry protective groups; Sp is absent or a carbonyl or thiocarbonyl radical; IA is a non-peptide radical addressing an αvβ3 integrin receptor, e.g., a radical of formula R18COCH2CHPhNHCOCH2NHCO-m-C6H4NH[C(:NH)NHR19]q, where R18 is OH, (un)substituted (cyclo)alkoxy, aryloxy, heterocyclyloxy, a direct bond, or an atom from the group N, O and S, via which the radical is bonded to the rest of the conjugate; q is 0 or 1; R19 is H, (un)substituted (cyclo)alkyl, aryl, heterocyclyl, an alkylamine or alkylamide radical, or a direct bond, via which the radical is bonded to the rest of the conjugate] and their physiol. acceptable salts and stereoisomers. The cytostatics have a tumor-specific action as a result of linkage to αvβ3integrin antagonists via preferred linking units which can be selectively cleaved by enzymes such as metallo matrix proteases (MMPs5), i.e., by enzymes which can especially be found in tumor tissue. The preferred linking units guarantee the serum stability of the conjugate of cytostatic and αvβ3 integrin antagonist and, at the same time, the desired intracellular action within tumor cells as a result of its specific enzymic or hydrolytic cleavability with release of the cytostatic. Thus, 20-O-[PrNHCONH-m-C6H4SO2NH-m-C6H4CH(CH2CO2H)NHCONH-p-C6H4NHC(S)-Pro-Leu-Gly-Leu-His-Val]camptothecin (1) was prepared by reaction of 20(S)-camptothecin with N-(tert-butoxycarbonyl)-L-valine-N-carboxyanhydride, deprotection, peptide coupling reactions, and formation of the thiourea linkage. Compound 1 was assayed for cytostatic action on human large intestine cell line HT29 (IC50 = 40 nM).

L3 ANSWER 11 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-90-1 REGISTRY
CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-histidyl-, 5-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C71 H81 N15 O15 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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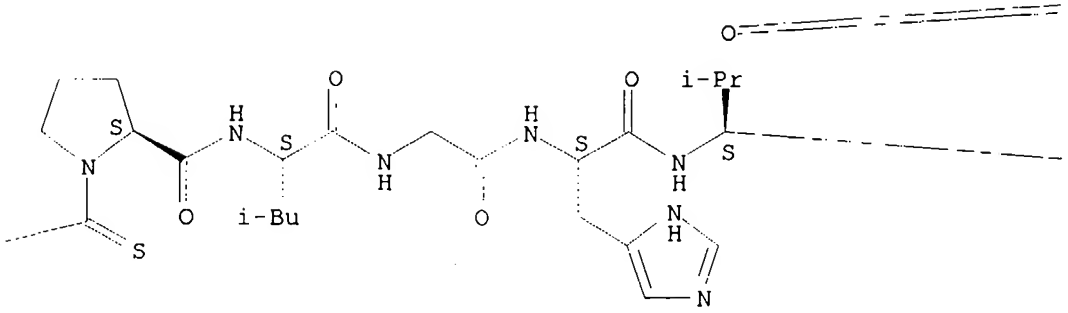

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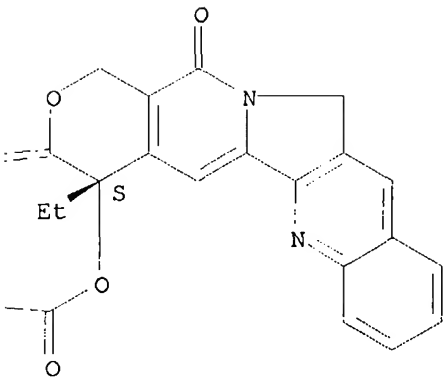


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:63479 Preparation of conjugates of integrin receptor antagonists and a cytostatic agent having specifically cleavable linking units. Lerchen, Hans-Georg; Baumgarten, Joerg; Lockhoff, Oswald; Albers, Markus; Schoop, Andreas (Bayer Aktiengesellschaft, Germany). Eur. Pat. Appl. EP 1219305 A1 20020703, 127 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2000-128401 20001227.

AB The invention relates to cytostatics CT-LI-Sp-IA [CT denotes a cytotoxic radical or a radical of a cytostatic or a cytostatic derivative which can addnl. carry a hydroxy, carboxy or amino group; LI is a linker group comprising 5- to 8-amino acid residues in the D- or L-configuration, which can each optionally carry protective groups; Sp is absent or a carbonyl or thiocarbonyl radical; IA is a non-peptide radical addressing an αvβ3 integrin receptor, e.g., a radical of formula R18COCH2CHPhNHCOCH2NHCO-m-C6H4NH[C(:NH)NHR19]q, where R18 is OH, (un)substituted (cyclo)alkoxy, aryloxy, heterocyclyloxy, a direct bond, or an atom from the group N, O and S, via which the radical is bonded to the rest of the conjugate; q is 0 or 1; R19 is H, (un)substituted (cyclo)alkyl, aryl, heterocyclyl, an alkylamine or alkylamide radical, or a direct bond, via which the radical is bonded to the rest of the conjugate] and their physiol. acceptable salts and stereoisomers. The cytostatics have a tumor-specific action as a result of linkage to αvβ3integrin antagonists via preferred linking units which can be selectively cleaved by enzymes such as metallo matrix proteases (MMPs5), i.e., by enzymes which can especially be found in tumor tissue. The preferred linking units guarantee the serum stability of the conjugate of cytostatic and αvβ3 integrin antagonist and, at the same time, the desired intracellular action within tumor cells as a result of its specific enzymic or hydrolytic cleavability with release of the cytostatic. Thus, 20-O-[PrNHCONH-m-C6H4SO2NH-m-C6H4CH(CH2CO2H)NHCONH-p-C6H4NHC(S)-Pro-Leu-Gly-Leu-His-Val]camptothecin (1) was prepared by reaction of 20(S)-camptothecin with N-(tert-butoxycarbonyl)-L-valine-N-carboxyanhydride, deprotection, peptide coupling reactions, and formation of the thiourea linkage. Compound 1 was assayed for cytostatic action on

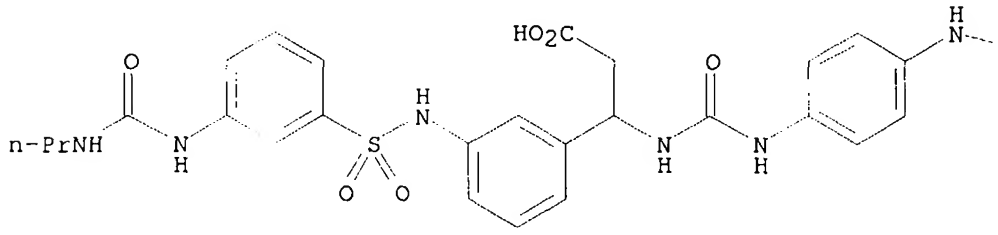
human large intestine cell line HT29 (IC50 = 40 nM).

L3 ANSWER 12 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-89-8 REGISTRY
CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-histidylglycyl-L-leucyl-L-asparaginyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C75 H87 N17 O17 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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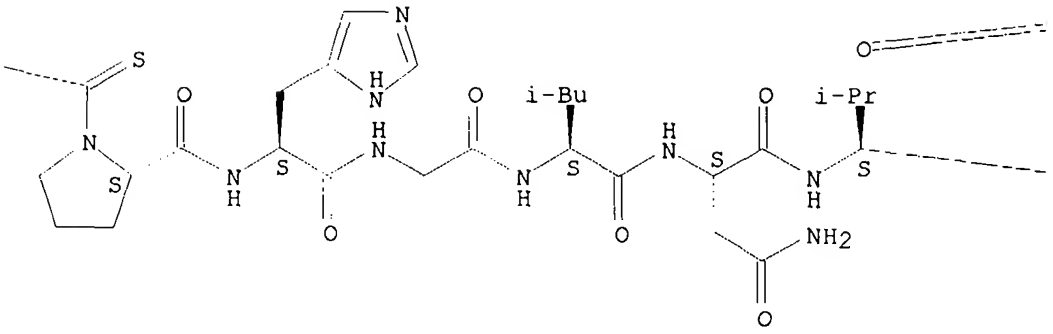

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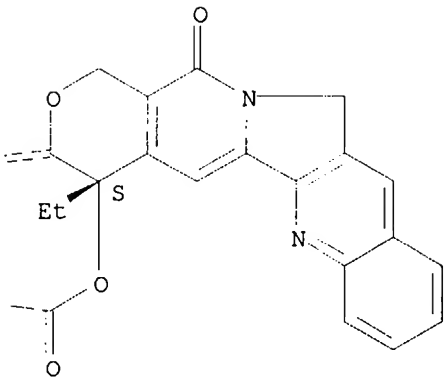

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1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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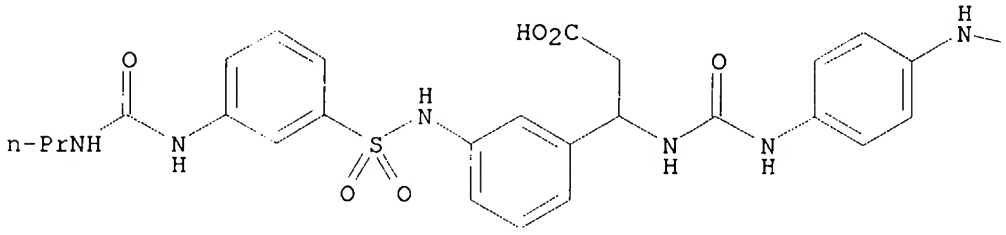
human large intestine cell line HT29 (IC50 = 40 nM).

L3 ANSWER 13 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-88-7 REGISTRY
CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolylglycylglycyl-L-leucyl-L-asparaginyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C71 H83 N15 O17 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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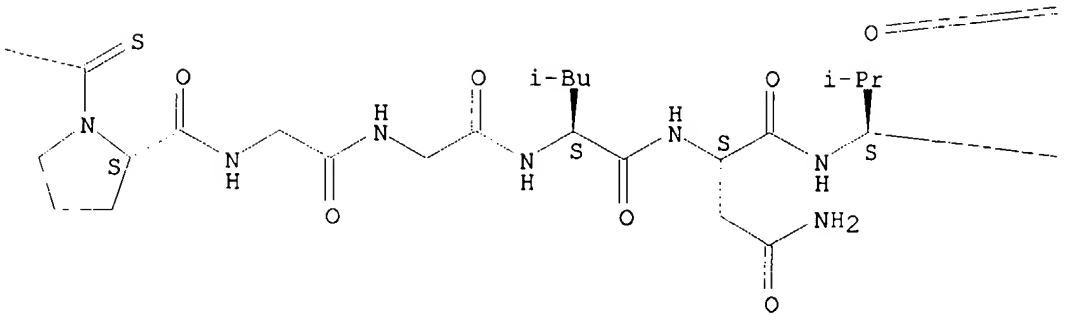

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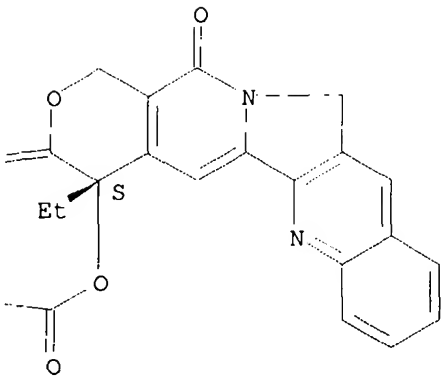

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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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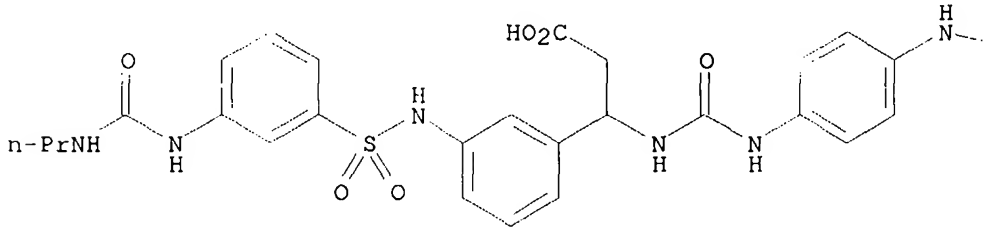
L3 ANSWER 14 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-86-5 REGISTRY
CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-norvalyl-L-asparaginyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C74 H89 N15 O17 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.

PAGE 1-A



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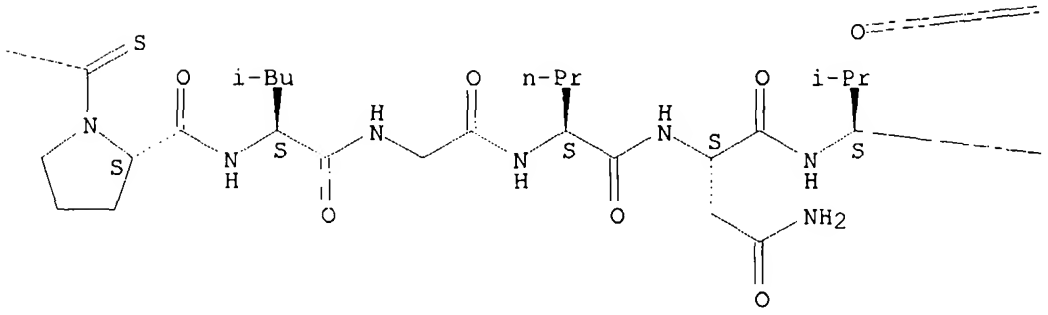

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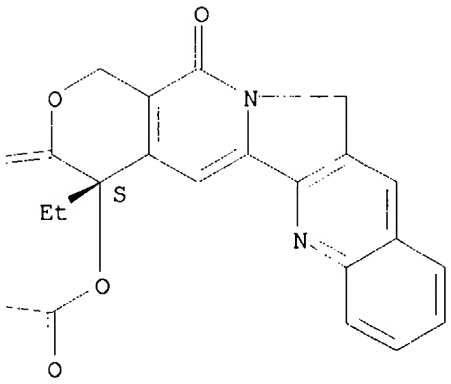

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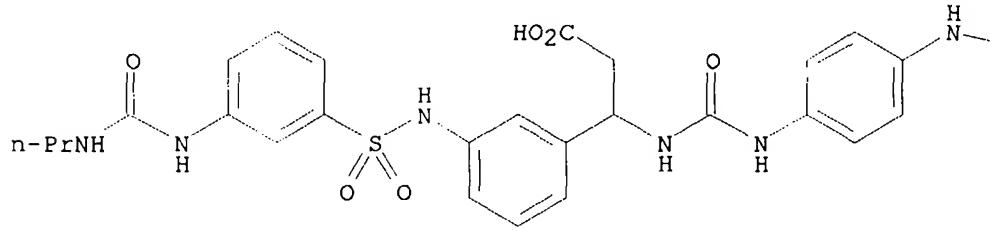
L3 ANSWER 15 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-85-4 REGISTRY
CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-L-lysyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C77 H97 N15 O16 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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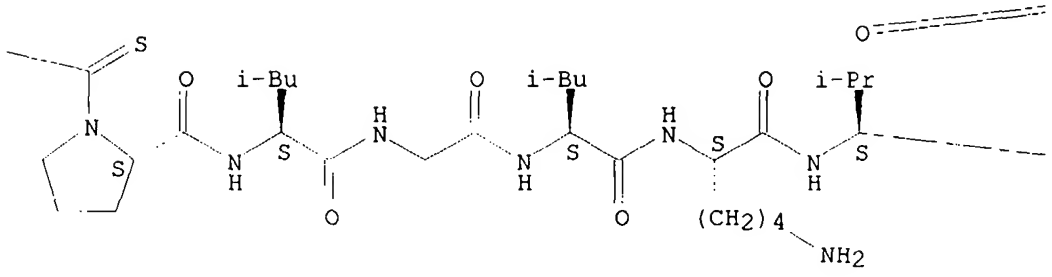

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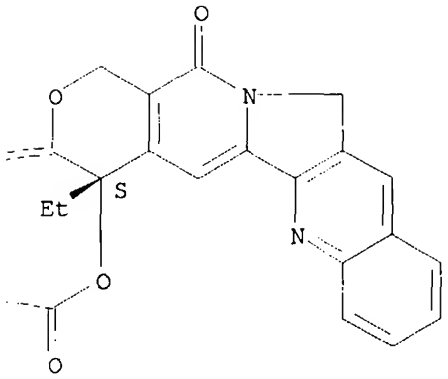

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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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AB The invention relates to cytostatics CT-LI-Sp-IA [CT denotes a cytotoxic radical or a radical of a cytostatic or a cytostatic derivative which can addnl. carry a hydroxy, carboxy or amino group; LI is a linker group comprising 5- to 8-amino acid residues in the D- or L-configuration, which can each optionally carry protective groups; Sp is absent or a carbonyl or thiocarbonyl radical; IA is a non-peptide radical addressing an αvβ3 integrin receptor, e.g., a radical of formula R18COCH2CHPhNHCOCH2NHCO-m-C6H4NH[C(:NH)NHR19]q, where R18 is OH, (un)substituted (cyclo)alkoxy, aryloxy, heterocyclyloxy, a direct bond, or an atom from the group N, O and S, via which the radical is bonded to the rest of the conjugate; q is 0 or 1; R19 is H, (un)substituted (cyclo)alkyl, aryl, heterocyclyl, an alkylamine or alkylamide radical, or a direct bond, via which the radical is bonded to the rest of the conjugate] and their physiol. acceptable salts and stereoisomers. The cytostatics have a tumor-specific action as a result of linkage to αvβ3integrin antagonists via preferred linking units which can be selectively cleaved by enzymes such as metallo matrix proteases (MMPs5), i.e., by enzymes which can especially be found in tumor tissue. The preferred linking units guarantee the serum stability of the conjugate of cytostatic and αvβ3 integrin antagonist and, at the same time, the desired intracellular action within tumor cells as a result of its specific enzymic or hydrolytic cleavability with release of the cytostatic. Thus, 20-O-[PrNHCONH-m-C6H4SO2NH-m-C6H4CH(CH2CO2H)NHCONH-p-C6H4NHC(S)-Pro-Leu-Gly-Leu-His-Val]camptothecin (1) was prepared by reaction of 20(S)-camptothecin with N-(tert-butoxycarbonyl)-L-valine-N-carboxyanhydride, deprotection, peptide coupling reactions, and formation of the thiourea linkage. Compound 1 was assayed for cytostatic action on human large intestine cell line HT29 (IC50 = 40 nM).

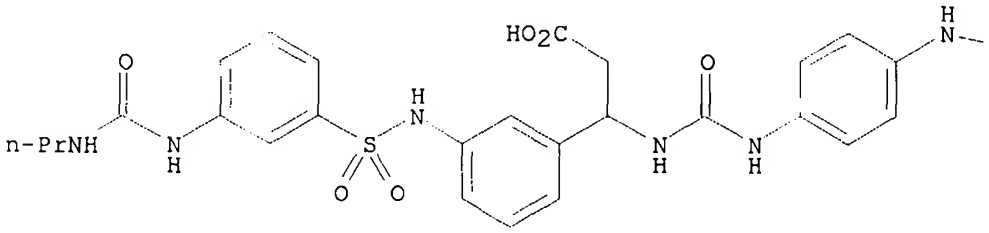
Searched by: Mary Hale 308-4258 CM-1 1E01

L3 ANSWER 16 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-84-3 REGISTRY
CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-S-methyl-L-cysteinyl-L-histidyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C75 H88 N16 O16 S3
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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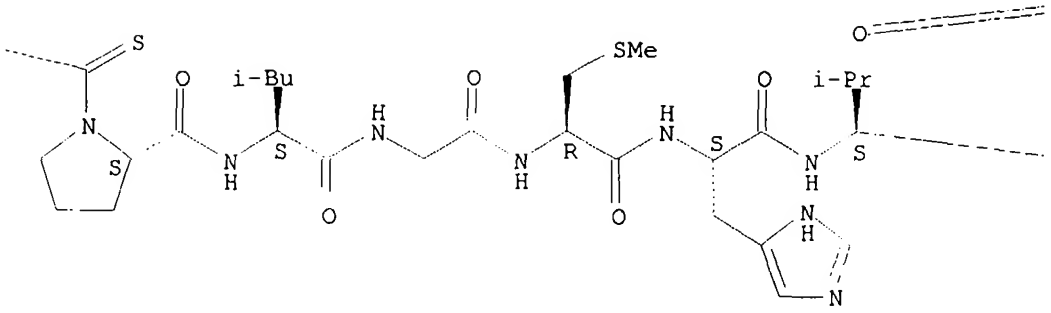
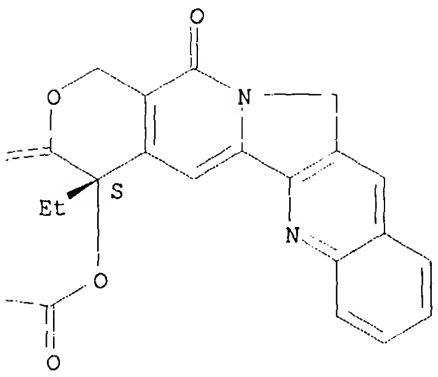


Searched by: Mary Hale 308-4258 CM-1 1E01



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:63479 Preparation of conjugates of integrin receptor antagonists and a cytostatic agent having specifically cleavable linking units. Lerchen, Hans-Georg; Baumgarten, Joerg; Lockhoff, Oswald; Albers, Markus; Schoop, Andreas (Bayer Aktiengesellschaft, Germany). Eur. Pat. Appl. EP 1219305 A1 20020703, 127 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2000-128401 20001227.

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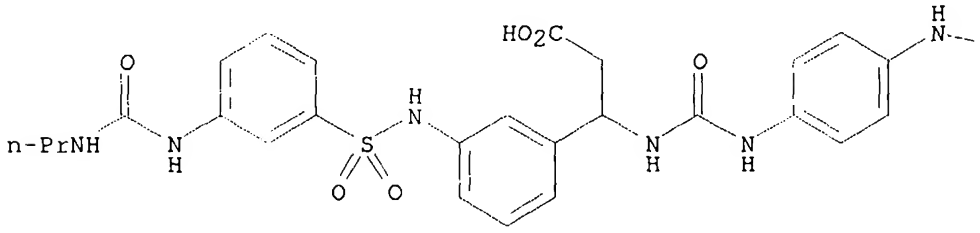
L3 ANSWER 17 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-79-6 REGISTRY
CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-L-tryptophyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C82 H95 N15 O16 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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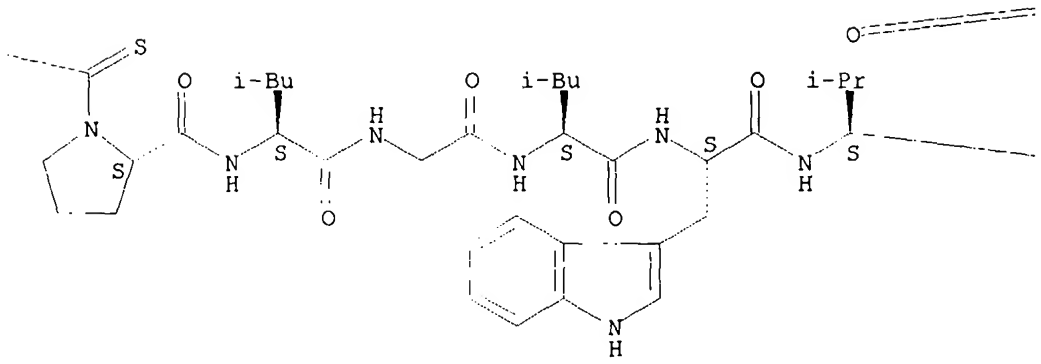
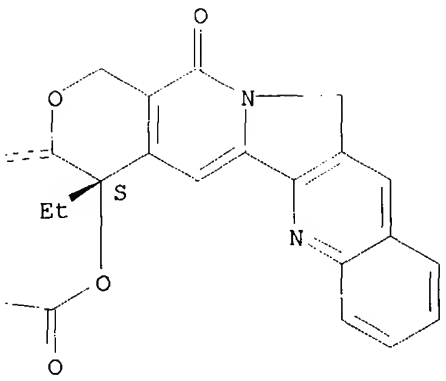


Searched by: Mary Hale 308-4258 CM-1 1E01



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:63479 Preparation of conjugates of integrin receptor antagonists and a cytostatic agent having specifically cleavable linking units. Lerchen, Hans-Georg; Baumgarten, Joerg; Lockhoff, Oswald; Albers, Markus; Schoop, Andreas (Bayer Aktiengesellschaft, Germany). Eur. Pat. Appl. EP 1219305 A1 20020703, 127 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2000-128401 20001227.

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L3 ANSWER 18 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-78-5 REGISTRY

Searched by: Mary Hale 308-4258 CM-1 1E01

CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-S-methyl-L-cysteinyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)

FS PROTEIN SEQUENCE; STEREOSEARCH

MF C75 H92 N14 O16 S3

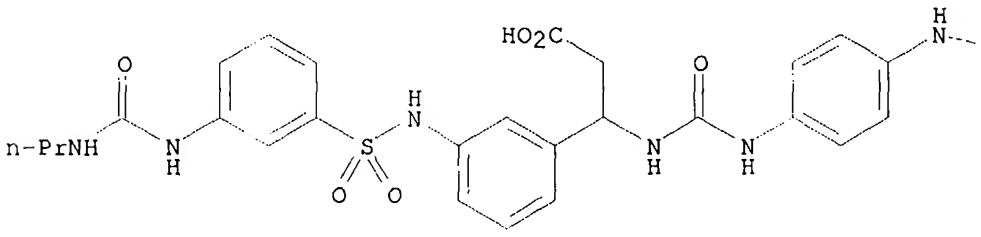
SR CA

LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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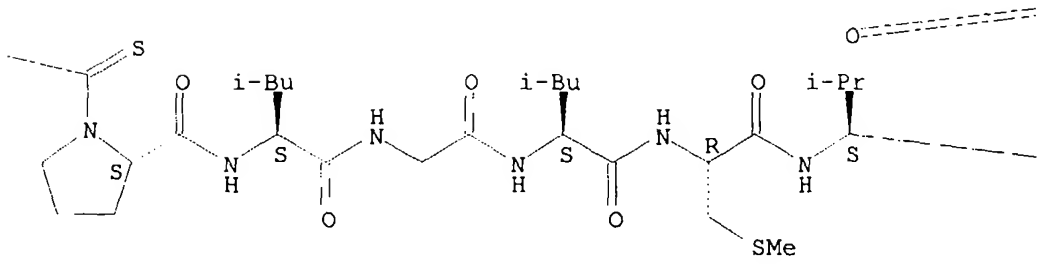
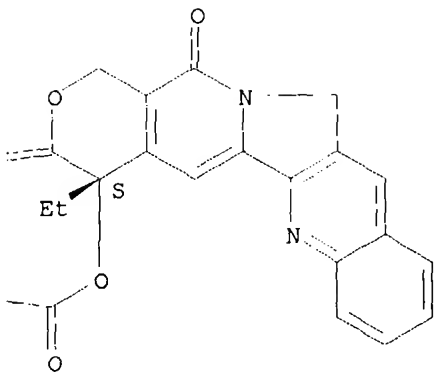


Searched by: Mary Hale 308-4258 CM-1 1E01



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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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L3 ANSWER 19 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-76-3 REGISTRY

Searched by: Mary Hale 308-4258 CM-1 1E01

CN L-Valine, 1-[[[4-[[[[(1S)-2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-L-asparaginyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)

FS PROTEIN SEQUENCE; STEREOSEARCH

MF C75 H91 N15 O17 S2

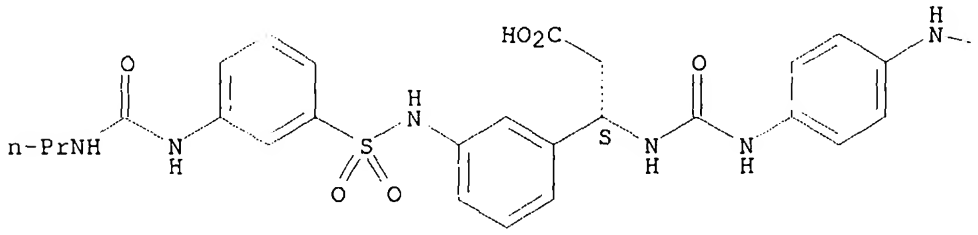
SR CA

LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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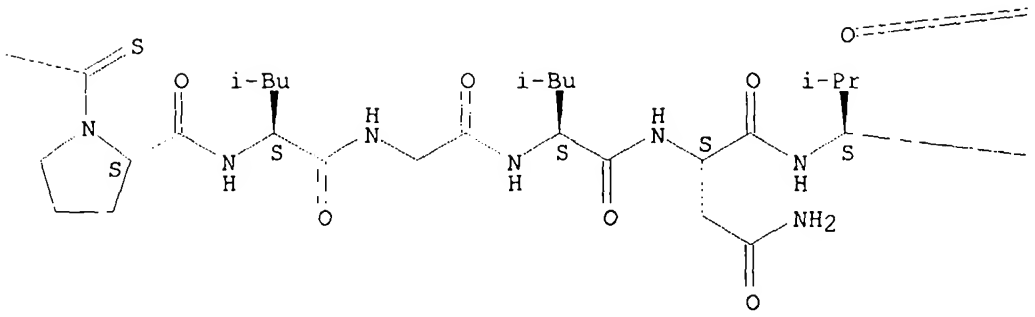
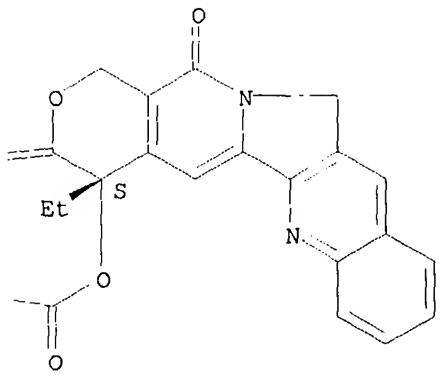


Searched by: Mary Hale 308-4258 CM-1 1E01



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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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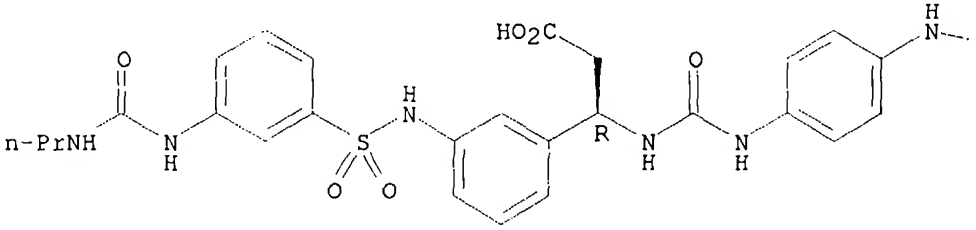
Searched by: Mary Hale 308-4258 CM-1 1E01

L3 ANSWER 20 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-75-2 REGISTRY
CN L-Valine, 1-[[[4-[[[[(1R)-2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-L-asparaginyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C75 H91 N15 O17 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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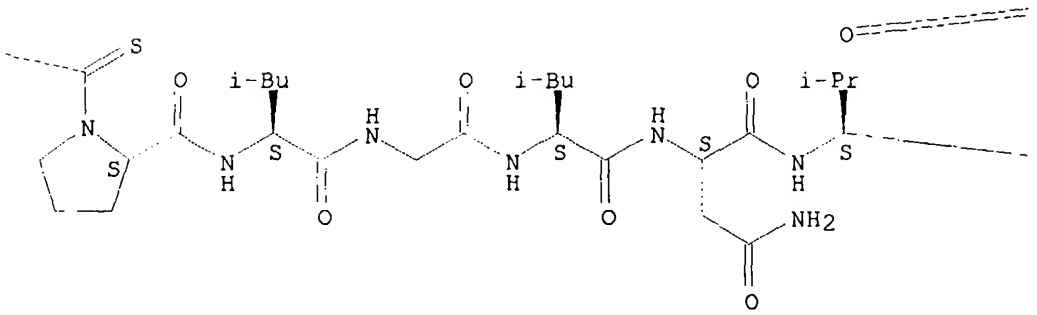

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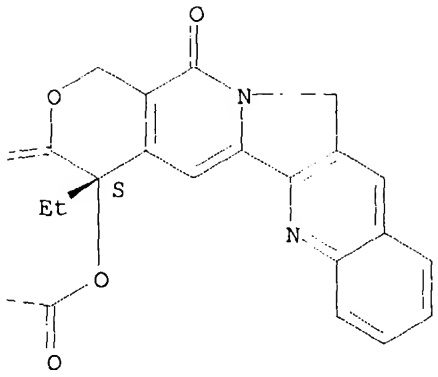

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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:63479 Preparation of conjugates of integrin receptor antagonists and a cytostatic agent having specifically cleavable linking units. Lerchen, Hans-Georg; Baumgarten, Joerg; Lockhoff, Oswald; Albers, Markus; Schoop, Andreas (Bayer Aktiengesellschaft, Germany). Eur. Pat. Appl. EP 1219305 A1 20020703, 127 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2000-128401 20001227.

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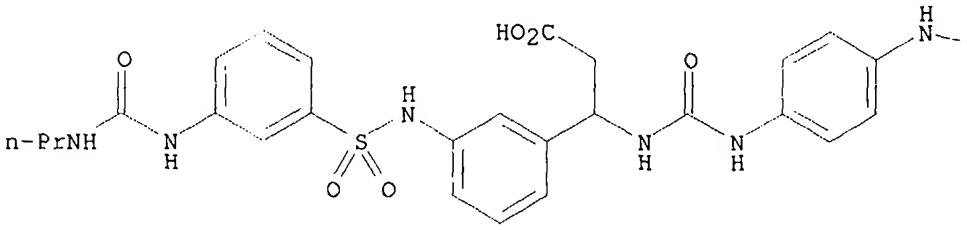
L3 ANSWER 21 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-74-1 REGISTRY
CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-L-asparaginyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C75 H91 N15 O17 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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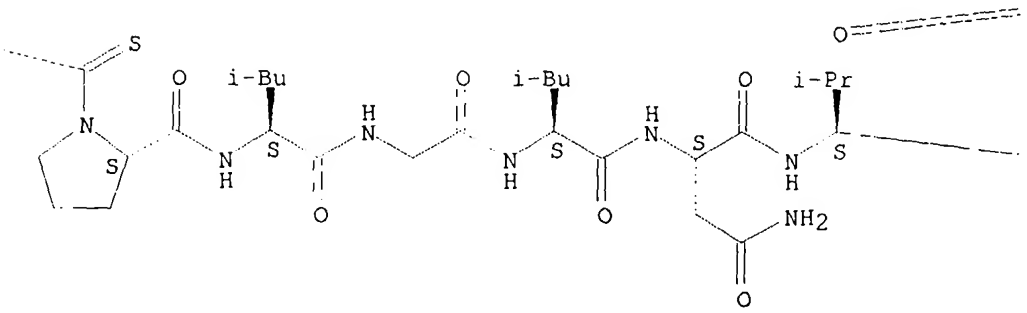

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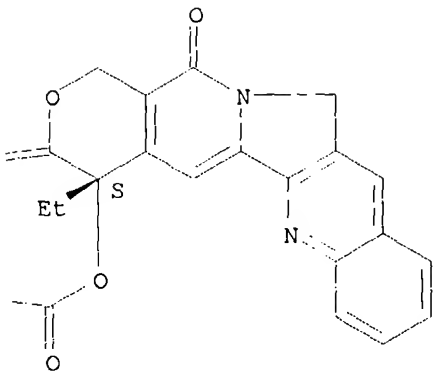

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:63479 Preparation of conjugates of integrin receptor antagonists and a cytostatic agent having specifically cleavable linking units. Lerchen, Hans-Georg; Baumgarten, Joerg; Lockhoff, Oswald; Albers, Markus; Schoop, Andreas (Bayer Aktiengesellschaft, Germany). Eur. Pat. Appl. EP 1219305 A1 20020703, 127 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2000-128401 20001227.

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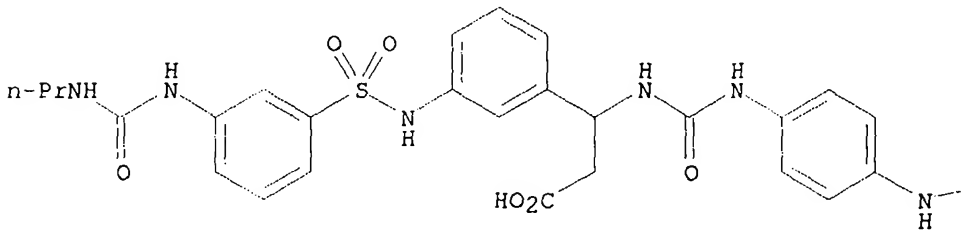
L3 ANSWER 22 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-73-0 REGISTRY
CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-, 5-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C71 H85 N13 O15 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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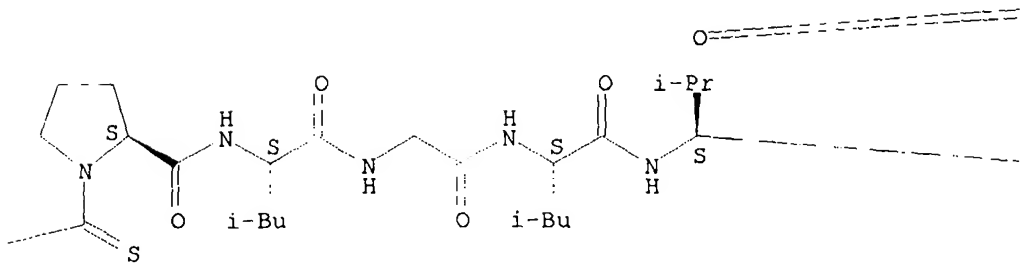

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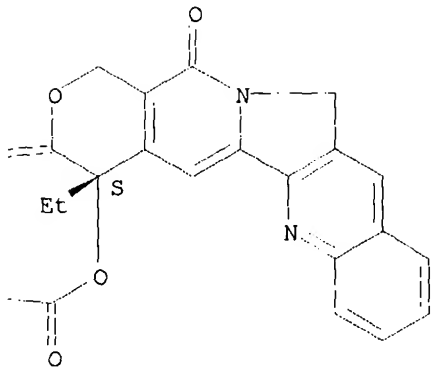

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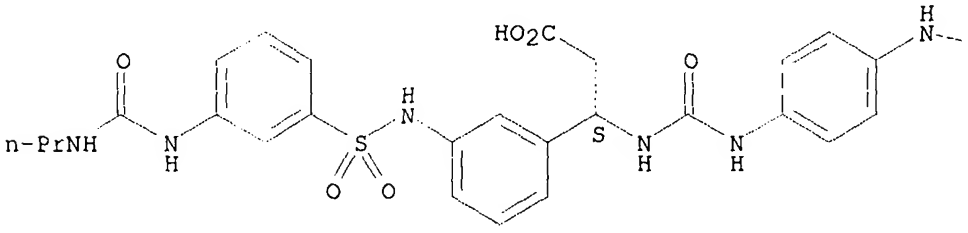
L3 ANSWER 23 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-68-3 REGISTRY
CN L-Valine, 1-[[[4-[[[[(1S)-2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-L-histidyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C77 H92 N16 O16 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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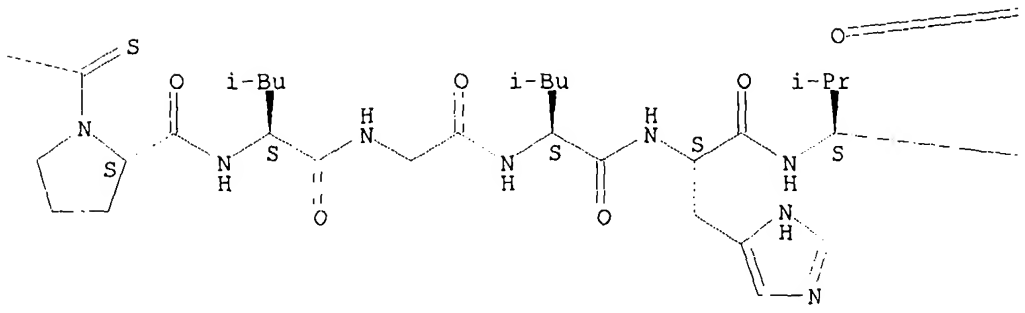

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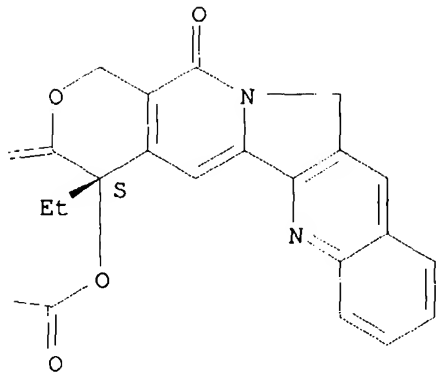

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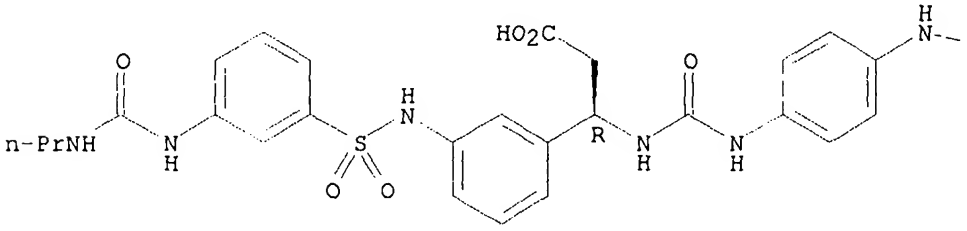
L3 ANSWER 24 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-67-2 REGISTRY
CN L-Valine, 1-[[[4-[[[[(1R)-2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-L-histidyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C77 H92 N16 O16 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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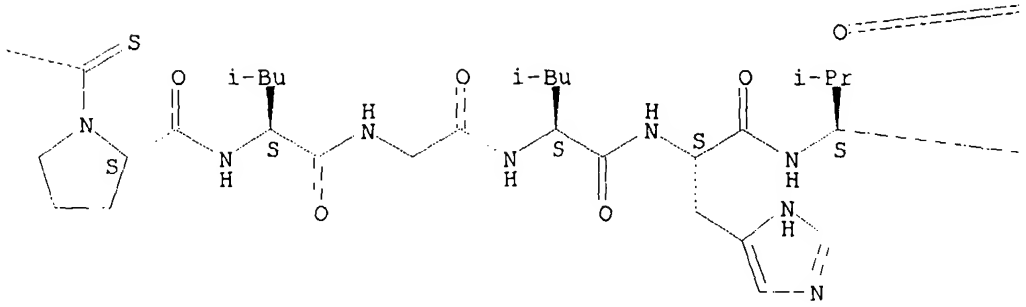

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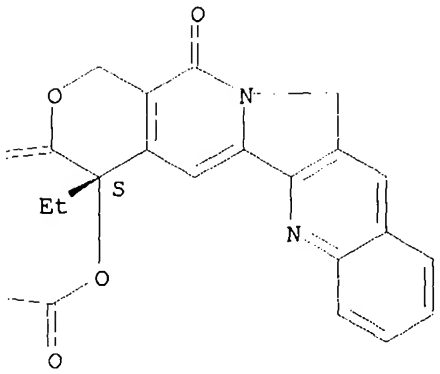

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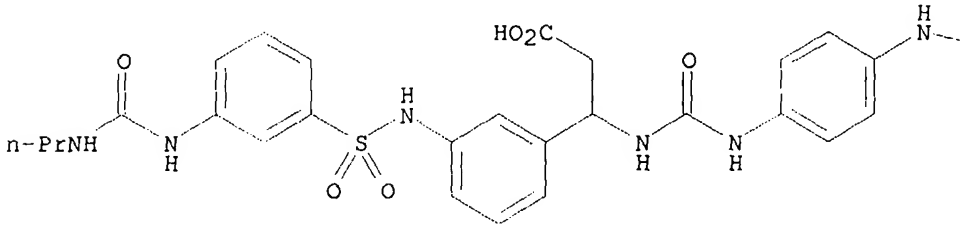
L3 ANSWER 25 OF 25 REGISTRY COPYRIGHT 2003 ACS on STN
RN 439864-66-1 REGISTRY
CN L-Valine, 1-[[[4-[[[[2-carboxy-1-[3-[[[3-[[(propylamino)carbonyl]amino]phenyl]sulfonyl]amino]phenyl]ethyl]amino]carbonyl]amino]phenyl]amino]thioxomethyl]-L-prolyl-L-leucylglycyl-L-leucyl-L-histidyl-, 6-[(4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl] ester (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C77 H92 N16 O16 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



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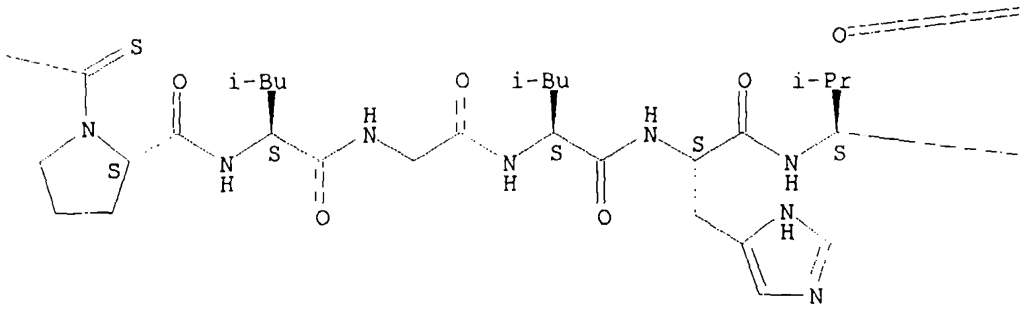

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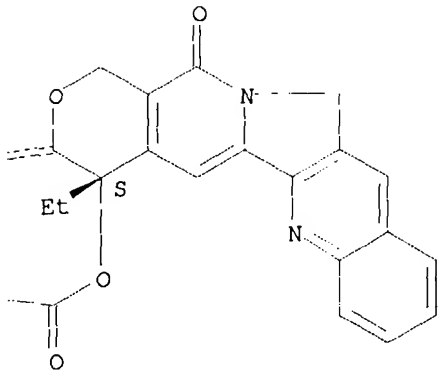

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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:63479 Preparation of conjugates of integrin receptor antagonists and a cytostatic agent having specifically cleavable linking units. Lerchen, Hans-Georg; Baumgarten, Joerg; Lockhoff, Oswald; Albers, Markus; Schoop, Andreas (Bayer Aktiengesellschaft, Germany). Eur. Pat. Appl. EP 1219305 A1 20020703, 127 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2000-128401 20001227.

AB The invention relates to cytostatics CT-LI-Sp-IA [CT denotes a cytotoxic radical or a radical of a cytostatic or a cytostatic derivative which can addnl. carry a hydroxy, carboxy or amino group; LI is a linker group comprising 5- to 8-amino acid residues in the D- or L-configuration, which can each optionally carry protective groups; Sp is absent or a carbonyl or thiocarbonyl radical; IA is a non-peptide radical addressing an αvβ3 integrin receptor, e.g., a radical of formula R18COCH2CHPhNHCOCH2NHCO-m-C6H4NH[C(:NH)NHR19]q, where R18 is OH, (un)substituted (cyclo)alkoxy, aryloxy, heterocyclyloxy, a direct bond, or an atom from the group N, O and S, via which the radical is bonded to the rest of the conjugate; q is 0 or 1; R19 is H, (un)substituted (cyclo)alkyl, aryl, heterocyclyl, an alkylamine or alkylamide radical, or a direct bond, via which the radical is bonded to the rest of the conjugate] and their physiol. acceptable salts and stereoisomers. The cytostatics have a tumor-specific action as a result of linkage to αvβ3integrin antagonists via preferred linking units which can be selectively cleaved by enzymes such as metallo matrix proteases (MMPs5), i.e., by enzymes which can especially be found in tumor tissue. The preferred linking units guarantee the serum stability of the conjugate of cytostatic and αvβ3 integrin antagonist and, at the same time, the desired intracellular action within tumor cells as a result of its specific enzymic or hydrolytic cleavability with release of the cytostatic. Thus, 20-O-[PrNHCONH-m-C6H4SO2NH-m-C6H4CH(CH2CO2H)NHCONH-p-C6H4NHC(S)-Pro-Leu-Gly-Leu-His-Val]camptothecin (1) was prepared by reaction of 20(S)-camptothecin with N-(tert-butoxycarbonyl)-L-valine-N-carboxyanhydride, deprotection, peptide coupling reactions, and formation of the thiourea linkage. Compound 1 was assayed for cytostatic action on human large intestine cell line HT29 (IC50 = 40 nM).

Searched by: Mary Hale 308-4258 CM-1 1E01

=> fil caol;s l3

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	252.85	253.06

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-15.50	-15.50

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L4 0 L3

=> fil hcaplus;s l3

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.40	253.46

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
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L5 1 L3

=> fil reg;save l1 meller/q

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.25	255.71

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 3 NOV 2003 HIGHEST RN 612478-18-9
DICTIONARY FILE UPDATES: 3 NOV 2003 HIGHEST RN 612478-18-9

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

QUERY L1 HAS BEEN SAVED AS 'MELLER/Q'

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.40	256.11

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-15.50

STN INTERNATIONAL LOGOFF AT 14:29:10 ON 05 NOV 2003

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